National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Acquired Immune Deficiency Syndrome
AIDS RESEARCH ADVISORY COMMITTEE

May 24, 2004
Bethesda, Maryland

Summary

The AIDS Research Advisory Committee (ARAC) met on Monday, May 24, 2004, from 1:00 to 8:00 p.m. Members present: Mr. Moises Agosto, and Drs. Hank Balfour, Deborah Birx (ex officio), Charles Davis, Lawrence "Bopper" Deyton, Ashley Haase, King Holmes (chair), Brooks Jackson, Harold Jaffe (ex-officio), Robert Johnston, Phyllis Kanki, Preston Marx, Andrea Ruff, Ruth Ruprecht, Nathan Thielman, and Jack Whitescarver (ex officio), and Reverend O'Brien. *Ad hoc* participants included Drs. Jorge Sanchez, Thomas Quinn, Cliff Lane and Mr. Martin Delaney. DAIDS staff members present included Drs. Edmund Tramont, Jon Kagan, Carl Dieffenbach, Peggy Johnston, Sandra Lehrman and Mr. Daniel Montoya and Mr. Matthew Murguia, and Ms. Rona Siskind (Executive Secretary).

Introductory Remarks

Ed Tramont, Director, Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), opened the meeting by recognizing the contributions of four members who are rotating off the committee: Drs. Balfour, Jaffe, R. Johnston, and Marx. He also introduced Dr. Deborah Birx, director of the U.S. Military HIV Research Program, who is joining ARAC as an ex officio member.

Dr. Tramont reported that the DAIDS is the only division-level unit of NIH dedicated to a single disease. Its mission includes research on (1) basic knowledge of HIV-AIDS, (2) treatment and care of HIV/AIDS patients and (3) vaccines and other prevention strategies. DAIDS has a staff of 168 scientists from 12 different countries of origin, 61 percent of whom are women. Its budget of $840 million represents about 30 percent of total NIH spending on AIDS and AIDS-related disease. DAIDS' research portfolio is divided evenly between basic and clinical research, with 25 percent going to unsolicited proposals and 75 percent to solicited proposals.

The clinical trials networks have played a vital role in DAIDS research, providing the critical mass and infrastructure for both quality and continuity in collaborative, protocol-driven clinical research. The networks have made significant contributions in areas including highly active antiretroviral therapy (HAART), mother-to-child transmission (MTCT), circumcision trials, research on vaccines and microbicides, and other cohort studies. The networks have enrolled over 60,000 volunteers and have led to the publication of over 1,000 scientific manuscripts.

However, the shifting dynamics of the AIDS epidemic, and the prospect of stable or declining budgets necessitate the reconfiguration or restructuring of the networks. They need to sponsor larger and longer-term studies, with a greater emphasis on vaccine and microbicide development and on behavioral interventions. In addition, the networks need to support and implement more studies in resource-poor regions of the developing world, where 97 percent of new cases now occur. In the future, the networks must not only expand the volunteer base and answer key scientific questions; they must also demonstrate that they are making efficient use of U.S. government resources.

To gather input and advice on this process, DAIDS has held numerous consultations with participants and stakeholders over the past three years. The present meeting represents the forty-eighth consultation, the goal of which is to review and seek ARAC's advice on the scientific priorities of DAIDS clinical research and how to reconfigure the networks to reflect those priorities in the face of a changing epidemic and flat budgets.

Update – DAIDS Integrated Scientific Priorities

Carl Dieffenbach, Director, Basic Research Program, explained that the mission of DAIDS is to perform research that will lead to the end of the AIDS epidemic. This calls for a comprehensive approach that will protect the uninfected and prevent disease in those who are exposed to the virus, as well as inform therapy and care for those who develop the disease. The highest priority, therefore, must be on preventing the spread of HIV, and the most efficient means of doing this is to develop an effective vaccine. The second priority is to stop the progression of disease in those who become infected with the virus, either by lowering the initial peak of viremia in acute infection or by lowering the subsequent "set point" in chronic infection. (Viral load is also emerging as an important factor in both transmission and progression.) Research to address these questions must be conducted in all populations – adults, mothers and infants, and adolescents – and thus must address barriers to enrolling those populations. These scientific priorities suggest six areas of emphasis for clinical research:

1. Vaccine research and development;
2. Therapeutics – translational research and drug development;
3. Therapeutics – optimization of clinical management;
4. Microbicide research and development;
5. Mother-to-child transmission; and
6. Prevention research.

Peggy Johnston, Director, Vaccine and Prevention Research Program, reported that *vaccine research and development* remains the number one priority of DAIDS, with the ultimate objective of finding a vaccine that will protect all persons against infection and progression, and protect the public against further transmission, in all places and against all clades of HIV. Three such vaccines will be in NIAID-supported Phase 2 trials by 2006, and a number of additional candidates are now in Phase 1 trials, including several that are multiclade and/or antienvelope. During the period 2006-2013, this vaccine development effort will need a clinical research mechanism that can pursue the following priorities:

- Conduct Phase 1 and 2 trials to evaluate and compare candidates, combinations and adjuvants, evaluate host factors that may impact outcome, and test innovative approaches (e.g., mucosal immunization, enhanced innate immunity);
- Conduct Phase 2b and 3 trials in the highest-risk populations, including women and minorities, and develop cohorts and collect epidemiological information for future studies;
- Evaluate immune response, including the development of methods to optimize signal, development and validation of new assays for pivotal trials and to measure the full breadth of induced immune responses, and implementation of QA/QC programs;
- Standardize and optimize trial designs to accelerate the pace of evaluation and ensure rapid licensing, both domestic and international.

DAIDS will play a key role in the Partnership for AIDS Vaccine Development (PAVE), a collaboration between the NIH, the Centers for Disease Control and Prevention (CDC) and the Department of Defense (DOD), and in the recently proposed "Global Vaccine Enterprise," which promises an alliance of multiple independent entities to develop and execute a global strategic plan. These and other collaborations can be of great importance in addressing the biggest problems in vaccine research and development, such as identifying the highest-risk populations, advanced product development and manufacturing, developing the necessary facilities and infrastructure for clinical trials, and training a larger cadre of scientists who do research instead of, or in addition to, service delivery. In addition, some individuals will become infected from their own behavior during a vaccine trial, and there will be an ethical obligation to follow these cases for the life of the patient, at greatly increased cost.

Sandra Lehrman, Director, Therapeutics Research Program, elaborated on the objectives of *translational research and drug development*, namely preventing progression and death from HIV disease, treating the complications of both HIV disease and antiretroviral therapies, preventing the transmission of HIV and emergence of drug-resistant varieties, and ultimately to "cure" HIV infection by eradicating the virus and eliminating reservoirs. She anticipated that the period between 2006 and 2013 will see the introduction of drugs against at least two new HIV targets, fixed-dose combinations that will become the standard of care, and progress in integrating therapies to enhance immunity. To accomplish this vision, investigators will need to identify new agents and move them rapidly from preclinical assays to multicenter clinical trials.

The clinical research agenda to meet these therapeutic challenges will give high priority to evaluating drugs active against new targets in HIV, including small molecule entry inhibitors, integrase inhibitors and maturation inhibitors, as well as immunotherapeutic interventions, such as therapeutic vaccines. Several such compounds are already in clinical trials. High priority will also be given to evaluating new therapies for patients with co-infections (e.g., hepatitis C, tuberculosis, malaria, papillomavirus). These studies will share three important areas of emphasis:

1. Testing new hypotheses generated by pathogenesis studies;
2. Conducting pharmacokinetics studies in children and adolescents, to facilitate licensing and optimize use; and

3. Integrating immune-based therapies into treatment regimens to exploit mechanisms of antiviral effect and immune reconstitution.

In response to questions, Dr. Lehrman added that many companies are involved in drug development, but they tend to concentrate narrowly on target populations and commercialization. In some cases the companies are too small to move the drug rapidly to IND. Consequently, DAIDS still has a vital role to play in drug discovery and development.

Dr. Lehrman then reviewed the clinical research priorities in the second area of therapeutics, namely the *optimization of clinical management.* The first priority is to study the effectiveness of new regimens, particularly those that incorporate agents with novel mechanisms of action or new treatment combination strategies. The second priority is to evaluate therapies for co-infections, including prophylaxis, acute treatment and interactions with antiretroviral agents. The third priority is to optimize therapies on the basis of safety, adherence, resistance, durability of response, and prevention of transmission. In all of these areas, the goal is to reduce viral load as soon as possible and to keep it as low as possible for as long as possible. As in the area of drug development, there are opportunities for NIAID to collaborate with its sister institutes, as well as other federal agencies and international partners (e.g., DOD, EU, WHO, CDC, WB etc.), in studies of malignancies, metabolic abnormalities, coinfections, and complications of ART and/or progressive HIV disease.

In response to questions, Dr. Lehrman added that clinical management research will incorporate studies of acutely infected individuals, particularly the role of early interventions in modifying viral set point, long-term outcomes and transmission rates. Long-term toxicity will be addressed in the comparison and optimization of therapies, as will pharmacogenomics – the role of individual and population genetic differences in coinfections and responses to therapy. Committee members suggested that NIAID collaborate with the National Institute of Mental Health (NIMH) in studies of adherence, and with international partners in studies of how to optimize the delivery of care. International partners could make a particularly valuable contribution to the development of priorities in such areas as cohort development, standardization of assays and data management.

Dr. Johnston returned to review the objectives of DAIDS *microbicide research,* which are to identify a microbicide that is safe and at least partially effective against HIV, to determine the correlates of short- and long-term safety, and to evaluate and optimize acceptability and adherence (behavior). By 2006, DAIDS will have launched efficacy trials of two candidate topical microbicides; additional candidates are in the pipeline. In collaboration with NIAID's Division of Microbiology and Infectious Diseases and other partners, DAIDS hopes to create a network capable of conducting all stages of microbicide research and development, focusing on products safe enough for daily use that incorporate multiple mechanisms of attack. Behavioral research will be a key component, as will rectal safety and the ability to dissociate delivery from intercourse. In response to questions, she added that some therapeutics might prove to be good preventatives, but that the focus of microbicide research will be on small Phase 2 trials that quickly demonstrate which candidates work.

Dr. Lehrman outlined the research objectives in *mother-to-child transmission* (MTCT), which are (1) to identify safe, practical and more effective approaches to further reduce MTCT, especially in resource-poor settings; (2) to define treatment options for both mother and child, both separately and as a unit; and (3) to provide technical knowledge to ensure the prolonged success of MTCT programs. One of the success stories in MTCT is the effectiveness of neviripine (NVP) in preventing transmission, and several trials are currently underway to evaluate the use of NVP to prevent transmission through breast feeding and to optimize combination ART in NVP-exposed babies. In addition, several new vaccines will soon be ready for testing in babies. Priorities for MTCT research in the years 2006-2013 will be to optimize treatment regimens, both for mothers who are not yet on ART drugs, and for mothers who are already taking them for their own care. In both cases, the goals will be to decrease transmission, minimize toxicity, prevent drug resistance, and simplify delivery of care. Another priority will be to evaluate the safety and pharmacokinetics of new drugs, combinations and vaccines in nonpregnant women, pregnant women and infants, both HIV-positive and HIV-negative. Partnerships with the National Institute of Child Health and Human Development (NICHD) and National Institute of General Medical Sciences (NIGMS) will be important in achieving these goals.

Finally, Dr. Johnston reviewed DAIDS' objectives in the area of *prevention research,* which are (1) to identify practical, safe and effective approaches to halt the spread of HIV, especially in the populations where it is spreading most rapidly, and (2) to evaluate the worldwide suitability and sustainability of those approaches. Clinical trials are already underway to evaluate several drug-based prevention strategies, the protective value of circumcision, and the future will see greater availability and use of both ART and voluntary counseling and testing in developing countries. HIV transmission is driven by patients with acute early infections, however, so the first priority for prevention research will be to identify and target those patients. ART in established or late-stage infection, like pre-exposure protection, would have a lower priority.

Dr. Dieffenbach returned to enumerate a number of cross-cutting principles that will inform and guide the implementation of priorities across these six areas of emphasis:

- Feed information about serocoverters in vaccine and prevention studies into the acute infection data base or studies;
- Identify the highest-risk populations, which will affect the size and cost of vaccine and prevention efficacy trials;
- Include behavioral interventions in all studies (in partnership with NIMH and National Institute of Drug Abuse);
- Study the role of host differences in outcomes;
- Refer HIV-positive patients from screening studies to research programs and/or treatment programs;
- Evaluate the role of host differences in outcomes;
- Weigh the development of mega-sites against the use of many small sites;
- Develop common laboratory and data management procedures in order to pool data and address questions that cannot be studied by a single group or site; and

- Identify underserved or disenfranchised populations and the barriers that prevent them from participating in clinical research, and develop strategies to overcome those barriers.

In the discussion and public comment that followed, the presenters explained that recent successes in some areas, such as PMTCT, have moved them down on the list of priorities, and other topics are being addressed through R01 grants and other mechanisms rather than through a clinical research network. However, DAIDS recognizes that some time-sensitive studies, even if they involve MTCT or prevention research, might need to be addressed sooner than priorities in vaccine development or therapeutics. One participant noted that operational research may be needed to address some of the questions arising from ongoing research, such as why so few babies are receiving neviripine in sub-Saharan Africa.

During the public comment period, Carol Treston of the Pediatric AIDS Clinical Trial Group (PACTG) suggested that neviripine may not be a silver bullet after all, since there are signs of resistance in some of the mothers. Ms. Treston encouraged that there be some flexibility in the research priorities outlined in the RFA and that pre-adolescents and younger aged populations be considered for inclusion in HIV vaccine trials. Mark Harrington of the Treatment Action Group asked whether clinical trials in domestic settings, even successful trials like the recent ACTG 384, are an appropriate model for international trials, particularly when this may mean delaying implementation of ART trials in resource-poor settings. Harrington asked whether the clinical trials network system is nimble enough to terminate trials that clearly are not going to succeed, and others asked whether the system was responsive enough to address some of these research priorities immediately, instead of waiting two years for the new RFAs.

There was broad agreement that the system should be more responsive, and that this could be accomplished by holding money back to ensure performance or to address new opportunities and by giving the network more freedom to start and stop trials in a more timely manner. Defunding non-performing sites has been particularly difficult, and mechanisms to better facilitate this are needed. Several speakers also urged DAIDS to seek more input from those on the ground in developing countries, who have a better idea of the needs and demands of clinical research in resource-poor settings.

Highlights from Review of SMART Study

Dr. Lehrman reported on the Strategies for Managing Antiretroviral Therapy (SMART) study, sponsored by DAIDS through the Community Programs for Clinical Research on AIDS (CPCRA). SMART compares two ART strategies: *viral suppression,* in which the ART drug is given continuously (regardless of CD4+ count) in order to keep viral load as low as possible, and *drug conservation,* in which the drug is administered when the CD4+ cell count falls below 250 and discontinued when it returns to 350. The SMART trial will enroll 6,000 participants over 3 to 5 years and will follow them for 6 to 9 years to measure outcomes. DAIDS conducted a programmatic review of the study after it had enrolled its first 1,000 subjects in order to evaluate its feasibility and scientific relevance and to identify accrual issues. Conclusions and recommendations of that review included the following:

- SMART does address important and relevant scientific questions.
- Investigators should take a closer look at issues of adherence and safety.
- There is continuing uncertainty about the baseline assumptions, which may impact the power and duration of the trial.
- Slow enrollment is a continuing concern. Investigators should recruit additional sites and should carefully monitor and report to DAIDS on accrual every six months.
- The Data Safety and Monitoring Board should address accrual and study feasibility at its November 2004 meeting.
- Neither major modification nor termination is recommended.

In response to questions, Dr. Lehrman reported that the study continues to miss its accrual projections despite the addition of new sites. Dr. Tramont said that DAIDS has had to add $12.5 million to the SMART budget during the current fiscal year to cover the rising costs of accrual and follow-up. Dr. Holmes observed that these issues illustrate the generic problem of what to do about potentially failing studies, as well as those that have negative outcomes: the longer the study continues, the more difficult it becomes to terminate it. However, the SMART study does have a sunset clause. DAIDS officials remain confident that the study will meet its accrual goals, particularly because 150 international sites will soon be opening.

Office of AIDS Research (OAR) *Ad Hoc* Working Group

Jack Whitescarver, Office of AIDS Research (OAR), NIH, reported that OAR hosted a meeting on May 19, 2004 to solicit scientific priorities and advice on restructuring the Division's clinical trial's networks from leaders of these networks as well as other in the United States, United Kingdom, France, and Africa, and community representatives. Selected participants were asked to articulate the comments and advice that came from that meeting. The resulting nine principles, which were presented by Dr. Lawrence "Bopper" Deyton, are not meant to replace DAIDS' current organizing concepts of therapeutics, vaccine research and prevention, but rather meant to guide the development of the RFA:

1. The highest priority science should drive the structure of the NIAID clinical trials endeavor, not the reverse. DAIDS must be the host to a variety of clinical research structures in order to address the highest priority science.
2. The scientific priorities for AIDS clinical research in therapeutics, vaccines and prevention should be articulated more clearly and reassessed annually.
3. In order to achieve objectivity and transparency, major clinical trials and standing networks should receive routine external review, and the results of those reviews should be integrated into network operations. ARAC is the logical group to sponsor these reviews.
4. Community involvement and participation must be routinely incorporated in all aspects of DAIDS-supported clinical research, as should evaluation of the effectiveness of community involvement.
5. Protocol development and implementation must be streamlined and appropriate to the science being conducted.

6. To provide better coordination and efficiency, and to avoid redundancy, strong incentives should be provided to encourage intra-country communication and collaboration among all similar resources (e.g., reference labs, support contracts, community input), whether they are supported by DAIDS or other sources.
7. Redundancy in network missions should be avoided, and duplication of network core resources should be minimized wherever possible through the use of common resources.
8. Training and capacity building must accompany research support, both for sites in the United States and for sites in resource-poor settings.
9. DAIDS clinical research funding should support appropriate levels of infrastructure and provide DAIDS-controlled incentives to support the direct cost of conducting clinical trials, with funds held in reserve as needed to ensure the conduct of approved clinical trials. An appropriate balance might mean one-third for infrastructure and two-thirds for the conduct of clinical trials.

Rationale and Draft Concept for Coordinated Clinical Research Networks

Jonathan Kagan, Deputy Director, DAIDS, presented the proposed structure of "linked and coordinated networks of scientific activities and sites," based on ideas and advice from hundreds of intramural and extramural colleagues, and informed by both the changing nature of the HIV/AIDS epidemic and the scientific priorities enunciated by DAIDS management and the OAR *Ad Hoc* Working Group. Overall coordination and accountability would be the responsibility of a *Managing Partners Committee* comprised of the principal investigators (PIs) of each network plus others appointed by the Director, NIAID. Assessments of productivity and efficiency, and advice on changing or competing priorities, would come from one or more *External Scientific Review Groups* that would be advisory to the managing partners, to the individual networks, and to NIAID and its NIH Institutes and Centers (IC) partners. A centralized *Community Partners Committee* would coordinate and elevate community input and participation, within and across networks. A centralized *Clinical Research Management Support contract* would coordinate resource utilization for greater efficiency and provide additional support for community needs, training, translation, capacity expansion, etc. Each site and network, as well as the overall program, will have its own *Evaluation Plan* stressing not only scientific productivity and operational efficiency, but also community integration, partnering and communications.

The networks themselves would be made up of three types of components, each of which would apply for its own NIAID funding: (cost estimates are based on current expenditures):
1. *Leadership Groups.* – Up to eight networks, variously sized and configured, whose objective would be to establish cooperative clinical trial groups and research priorities for the conduct of HIV vaccine, therapeutic and prevention trials. Funding under the U01 mechanism is proposed for seven years, which will require NIH approval, with first-year costs estimated at $210 million to $280 million. The leadership of each of these groups (and others) would comprise the membership of the Managing Partners Committee.
2. *Domestic Sites.* – Approximately 50 and 65 domestic units that would become components of one or more clinical trial networks with which they have aligned based on

the proposed scientific agenda. Funding under the U01 mechanism would also be for seven years, with first-year costs estimated at $38 million to $100 million.

3. *International Sites.* – Between 25 and 40 international units that would likewise become components of one or more networks with which they have aligned based on the proposed scientific agenda. Funding would also be under the U01 mechanism for seven years, with first-year costs estimated at $12.5 million to $30 million.

Each leadership group, with its affiliated sites, would constitute a *Coordinated Clinical Research Network.*

Grant applications for Leadership Groups would specify the group's scientific agenda (one or more of the six DAIDS areas of emphasis outlined above), as well as the principal investigator, core elements, and preferred sites (domestic and/or international). Applications from individual sites (domestic or international) would be similar, specifying the principal investigator, research agenda, populations, and trial capacity, as well as preferred partner sites (including other ICs) and network affiliation(s). Individual sites would have separate funding streams for core resources and protocol costs, in order to provide greater flexibility. Funds would also be held back at the network and central levels to supplement individual sites, based on performance and opportunities.

Dr. Kagan described the resulting system as "flexible by design," structured in such a way as to bring people and sites together around central scientific questions, the activity being more important than the structure. Since no single research system can or should do every conceivable variety of clinical trial, this new system is intended to complement other existing programs/networks, and DAIDS would continue to accept and fund unsolicited grant applications for non-network clinical trials.

Discussion

In the discussion that followed, committee members asked where the money would come from for this expansion of the clinical trials networks. At present, there is no new money in the DAIDS budget to implement this proposal, but the proposed budget mechanisms will make it easier for DAIDS to move money out of unproductive areas and into areas where scientific opportunities exist in a timely fashion; extra money will be forthcoming from Congress only in response to proven performance. Others noted that, by decreasing isolation and increasing synergy, the proposal will make it easier for sites and networks to seek funding from other groups. Several members suggested that HHS and NIH examine how the other half of the HIV research budget is spent, and perhaps leverage additional money from those areas. However, this topic was beyond the scope of the meeting and this committee.

Because sites and networks will be coordinating their activities at the pre-application stage, this approach will reduce discord as well as duplication among competing networks. On the other hand, two networks that address the same questions in separate populations would be complementary, rather than redundant, and there could be positive value in "overlap" among vaccine, therapeutic and prevention research within a coordinated clinical trial network. Dr.

Kagan added that DAIDS will be able to compare the resulting portfolio with its research priorities, and to negotiate or re-solicit applications to create new sites and/or networks to address gaps or new opportunities. Several members noted favorably that the proposal gives both domestic and international sites greater autonomy and opportunity, particularly the separation of infrastructure from protocols.

Participants noted that the proposed system would address acknowledged problems, such as inertia and risk-aversion, but they questioned whether existing groups would have the motivation to change. Dr. Kagan indicated that existing groups and networks would be free to reapply, and that a consensus has already emerged among them that change is needed and that failure to change would be considered inefficient and ineffective. Some members worried that the proposal would create new layers of oversight and review, but Dr. Kagan assured them that the role of the Managing Partners Committee was not to review proposals, and hence not to fight over money, but rather to set priorities, share lessons, communicate intentions and facilitate partnerships. The need for inter-network coordination will be intense, because the number of networks will be constantly changing, and many sites will be partners in multiple networks.

Committee members praised the proposal for its elegance and agreed that it would make the DAIDS clinical research effort more nimble and responsive, but they wanted assurances that money would follow performance, whether that leads to protocols or core resources. Members seriously questioned the rationale for 7 years of funding rather than 5 years of funding, especially in view of the planned restructuring and need to critically re-evaluate the success of reorganized clinical trials networks. Several members expressed concern that the networks would not do the very long-term, large-scale operational research or the short-term, smaller-scale operational and applied clinical research that will be a necessary complement to vaccine, therapeutic and prevention research. Others observed that the peer review for this system will be a staggering undertaking, and that it will be challenging to develop appropriate evaluation criteria for all the different components of the system, particularly the international sites.

During the public comment period, David Munroe, the chair of the Community Constituency Group, Community Programs for Clinical Research on AIDS (CPCRA), recommended that greater community participation be mandated at all levels and at all sites, both domestic and international. He also urged DAIDS not to ignore therapeutic trials, which promise immediate benefit to those already living with HIV/AIDS, in favor of vaccine and prevention trials in resource-poor settings. As an HIV-positive taxpayer, he urged DAIDS to focus on its domestic agenda and suggested that international programs should spend money only in the poorest countries. Since the devil is often in the details, he awaits further particulars on the draft proposal, particularly with regard to the membership of the Community Partners Committee.

Daniel Montoya distributed compilations of comments on the draft concept that had been received as of May 10, 2004. Some comments were highly critical, others highly favorable, some general, others highly focused. DAIDS provided these comments to ARAC in order to inform their deliberations, and they will be used in the future to shape the three RFAs as they are

written. DAIDS has a mechanism on its website to accommodate additional comments, and they welcome additional comments.

Dr. Tom Quinn, *ad hoc* participant and reviewer, complimented the DAIDS staff on an excellent presentation of the draft concept, and raised four issues that will require particular attention as the proposal goes forward:

1. How to sort out competing scientific priorities among the groups that emerge;
2. How to balance domestic vs. international scientific issues as well as the balance of both international and domestic sites and protocol development development, enrollment and their full participation in the whole scientific endeavor;
3. How best to avoid duplication of resources; and
4. Holding back at least some of the funding for new ideas and emerging opportunities.

Strong leadership will be required to deal with these issues, and the External Scientific Review Group will likely have an important role in that regard.

Dr. King Holmes summarized the discussion and the key points still requiring attention from DAIDS staff:

- Defining optimal strategies for balancing fixed infrastructure costs, incremental per protocol infrastructure and staffing costs, and variable per case costs, to incentivize efficient protocol adoption and implementation, and to empower leadership to direct funds towards productive clinical sites. Consider industry standards in setting the balance, and allocate incremental and variable costs only when protocols are implemented;
- Managing/avoiding redundancy in core resources to ensure efficiency;
- Developing and publishing appropriate criteria for evaluating responses to the RFA and the networks themselves once they are formed and operational;
- Determining what additional technical and administrative staff at DAIDS are needed to manage the Clinical Research Management Support contract;
- Developing and managing the partnerships among NIAID and its sister ICs, and the role of OAR in brokering these “joint ventures in clinical trials research;”
- Developing and managing the collaborations between DAIDS and non-NIH funded agencies/organizations in clinical trials research;
- Finding mechanisms to create/foster both large centers of excellence and smaller sites with lower infrastructure costs that can help reach enrollment targets as needed;
- Defining mechanisms for peer review and funding of basic and clinical research that utilizes the clinical trials network infrastructure;
- Clarifying the scope of “optimizing clinical management” and its relationship to operational and applied clinical research; addressing the need to support locally-defined research needs and priorities, especially to support scale-up care and treatment in resource poor settings;
- Clarifying the scope of “prevention research” that is not covered by vaccine, microbicide, or PMTCT research, and further developing the prevention research agenda to be supported by the clinical trials networks.;

- Reflecting the principles put forward by the OAR Ad Hoc Working Group, particularly the idea that the highest priority science should drive the structure of the networks;
- Reassessing the NIAID priorities for clinical trials research on an annual basis, based on the annual NIH plan for HIV-related research and the role of ARAC in that review process;
- Implementing an external review of the progress of the networks, possibly every 12-18 months, perhaps by ARAC supplemented by *ad hoc* US and international clinical trials experts;
- Streamlining protocol development and implementation and including this as an evaluation criteria in the leadership group RFA.

Dr. Holmes asked for a motion to defer ARAC's action on the draft concept, allowing DAIDS the opportunity to respond to the committee's concerns and comments. The formal ARAC vote on the concepts would then occur by the full committee via teleconference later this summer. This recommendation was moved, seconded and agreed to unanimously. The meeting adjourned at 8:00 p.m.

King Holmes, M.D., Ph.D.
Chair, AIDS Research Advisory Committee

Edmund Tramont, M.D.
Director, Division of AIDS